IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Appellant	:	Joel S. Greenberger, et al.
Filed	:	April 14, 1999
Art Unit	:	1797
Examiner	:	William H. Beisner
Docket No.	:	PITT-1 DIV
Title of the Invention	:	METHOD AND APPARATUS FOR HOLDING CELLS

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APPEAL BRIEF

Sir:

This is an appeal brief from the Final Rejection dated April 2, 2009, for the above-identified patent application.

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I. Real Party in Interest

The real party in interest in the above-identified patent application is the Assignee of all the inventors, University of Pittsburgh.

II. Related Appeals and Interferences

The undersigned attorney is not aware of any related appeals or interferences which will directly affect or be directly affected by, or have a bearing on, the Board's decision in this pending appeal.

III. Status of Claims

Claims 1, 47-64, 70, 74-81, 86-97, 99, 100, 103, 104 and 114-127 are pending in the present application. They all have been finally rejected by the Examiner, and are the subject of this appeal.

Claims 2-40, 41-46, 65-69, 71-73, 82-85, 98, 101, 102 and 105-113 have been canceled.

IV. Status of Amendments

A Final Rejection was issued by the Examiner on April 2, 2009. An Amendment Under Rule 116 (Request for Reconsideration) was filed on September 2, 2009. In an Advisory Action dated September 23, 2009, the Examiner stated that the Request for Reconsideration has been considered but does not place the application in condition for allowance because of the reasons set forth in the Continuation Sheet which states, "Modification of the system of Bisconte would merely (emphasis added) involve reprogramming the system components such that the cell scanning cytometry of Price can be performed using image analysis and culture control."

There are no unanswered amendments in the application, nor any Office Actions having unanswered responses.

V. Summary of the Claimed Subject Matter

Claims 1, 51, 57, 70, 74, 75, 80 and 114 are independent claims. All dependent claims having means plus function language that are separately patentable are also listed.

Independent Claim 1 pertains to an apparatus for incubating and determining the state of individual cells within a plurality of cells. The apparatus comprises means 200 (page 12, lines 5-21, figure 1a) for incubating the plurality of cells. The incubating means 200 is a dynamically controlled closed environment in which the cells are grown and remains closed while it is dynamically controlled, which is maintained in a desired condition and in which each individual cell of the plurality of cells can be individually examined over time while the environment is dynamically controlled and maintained in the desired condition (page 11, lines 22-26). The incubating means 200 including an environment controlling means 216 (figure 1b, page 13, line 17 through page 14, line 7) for dynamically controlling the closed environment of the incubating means 200 (page 13, lines 18 and 19). The apparatus also comprises means 202 (page 12, line 22 through page 13, line 6; page 13, lines 11-16; page 24, lines 15-24; page 27, line 21 through page 30, line 9, figure 1a, figure 4c, figure 6) for automatically determining the state of said individual cell of the plurality of cells over time disposed in the incubating means 200 while the environment is dynamically controlled and maintained in the desired condition. The determining means 202 is in communication with the incubating means 200 (page 12, lines 1 and 2). The determining means 202 includes a computer 42 for automatically determining the state of said individual cell of the plurality of cells over time (page 12, lines 25-27).

Independent Claim 51 pertains to an apparatus for incubating and determining the state of individual cells within a plurality of cells. The apparatus comprises means 200 (page 12, lines 5-21) for incubating the plurality of cells, the incubating means 200 is a dynamically controlled closed environment in which the cells are grown and remains closed while it is dynamically controlled, which is maintained in a desired condition and in which each individual cell of the plurality of cells can be examined in real time over time while the environment is dynamically controlled and maintained in the desired condition (page 11, lines 22-26), the incubating means 200 including an environment controlling means 216 (page 13, line 17 through page 14, line 7) for dynamically controlling the closed environment of the incubating means 200 (page 13, lines 18 and 19). The apparatus comprises means 202 (page 12, line 22 through page 13, line 6; page 13, lines 11-16; page 24, lines 15-24; page 27, line 21 through page 30, line 9, figure 1a, figure 4c, figure 6) for automatically determining the state of said individual cell of the plurality of cells in real time (page 16, line 4) over time disposed in the incubating means 200. The determining means 202 is in communication with the incubating means 200 while the environment is dynamically controlled and maintained in the desired condition (page 12, lines 1 and 2). The determining means 202 includes a computer 42 for automatically determining the state of said individual cell of the plurality of cells in real time over time (page 12, lines 25-27).

Independent Claim 57 pertains to an apparatus for incubating and determining the state of individual cells within a plurality of cells. The apparatus comprises means 200 (page 12, lines 5-21) for incubating the plurality of cells, the incubating means 200 is a dynamically controlled closed environment in which the cells are grown and remains closed while it is dynamically

controlled, which is maintained in a desired condition and in which each individual cell of the plurality of cells can be examined over time while the environment is dynamically controlled and maintained in the desired condition (page 11, lines 22-26), the incubating means 200 including an environment controlling means 216 (figure 1b, page 13, line 17 through page 14, line 7) for dynamically controlling the closed environment of the incubating means 200 (page 13, lines 18 and 19). The apparatus also comprises means (page 12, line 23 through page 13, line 6; page 13, lines 11-16) for automatically tracking and identifying division and differentiation of said individual cell from the plurality of cells over time in the incubating means 200. The incubating means 200 is in communication with the tracking and identifying means (page 12, line 23; page 16, line 5; page 21, lines 20 and 21), the tracking and identifying means including a computer 42 for automatically tracking and identifying division and differentiation of said individual cell from the plurality of cells over time (page 12, lines 25-27).

Independent Claim 70 pertains to an apparatus for incubating and determining the state of individual cells within a plurality of cells. The apparatus comprises means 200 (page 12, lines 5-21) for incubating a first cell and at least a second cell amongst the plurality of cells (page 12, lines 5 and 6), the incubating means 200 is a dynamically controlled closed environment in which the cells are grown and remains closed while it is dynamically controlled, which is maintained in a desired condition and in which the first cell and at least the second cell can be individually examined over time amongst the plurality of cells while the environment is dynamically controlled and maintained in the desired condition (page 11, lines 22-26), the incubating means 200 including an environment controlling means 216 (figure 1b, page 13, line 17 through page

14, line 7) for dynamically controlling the closed environment of the incubating means 200 (page 13, lines 18 and 19). The apparatus also comprises means (page 24, lines 15-24; page 27, line 21 through page 30, line 9, figure 1a, figure 4c, figure 6) for individually controlling automatically the division and differentiation of the first cell and at least the second cell amongst the plurality of cells while the cells are in the incubating means 200. The controlling means automatically controls the division and differentiation of the first cell differently from the way it controls the division and differentiation of the second cell amongst the plurality of cells while the cells are in the incubating means 200. The controlling means is in communication with the incubating means 200 (page 14, lines 3-7). The apparatus also comprises means (page 12, line 23 through page 13, line 6; page 13, lines 11-16) for individually tracking and identifying division and differentiation automatically of the first cell and at least the second cell amongst the plurality of cells over time in the incubating means 200, the tracking and identifying means in communication with the incubating means 200, the tracking and identifying means including a computer 42 for individually tracking and identifying division and differentiation automatically of the first cell and at least the second cell amongst the plurality of cells over time (page 12, line 23; page 16, line 5; page 21, lines 20 and 21).

Independent Claim 74 pertains to an apparatus for incubating and determining the state of a stem cell within a plurality of cells. The apparatus comprises means 200 (page 12, lines 5-21) for incubating the plurality of cells, the incubating means 200 is a dynamically controlled closed environment in which the cells are grown and remains closed while it is dynamically controlled, which is maintained in a desired condition and in which each individual cell of the plurality of

cells can be individually examined over time while the environment is dynamically controlled and maintained in the desired condition (page 11, lines 22-26). The incubating means 200 includes an environment controlling means 216 (figure 1b, page 13, line 17 through page 14, line 7) for dynamically controlling the closed environment of the incubating means 200 (page 13, lines 18 and 19). The apparatus also comprises means 202 (page 12, line 22 through page 13, line 6; page 13, lines 11-16, page 24, lines 15-24; page 27, line 21 through page 30, line 9, figure 1a, figure 4c, figure 6; page 32, lines 16-29) for automatically determining a desired state of the stem cell (page 15, line 9) within the plurality of cells over time in the incubating means 200. The determining means 202 is connected to the incubating means 200, the determining means 202 in communication with the incubating means 200 (page 12, lines 1-3), the determining means 202 including a computer 42 for automatically determining a desired state of the stem cell within the plurality of cells over time (page 12, lines 25-27). The apparatus comprises means 230 (page 24, lines 5-14) for automatically introducing quiescence media to the stem cell within the plurality of cells in the incubating means 200 when the stem cell is in the desired state to inhibit the proliferation or selected differentiation of the stem cell in the incubating means 200, said introducing means connected to the incubating means 200, the introducing means in communication with the incubating means 200 (page 24, lines 5-7).

Independent Claim 75 pertains to an apparatus for incubating and determining the state of individual cells within a plurality of cells. The apparatus comprises means 200 (page 12, lines 5-21) for incubating the plurality of cells, the incubating means 200 is a dynamically controlled closed environment in which the cells are grown and remains closed while it is dynamically

controlled, which is maintained in a desired condition and in which each individual cell of the plurality of cells can be individually examined over time while the environment is dynamically controlled and maintained in the desired condition (page 11, lines 22-26). The incubating means 200 has means 216 (figure 1b, page 13, line 17 through page 14, line 7) for controlling the environment about said individual cell over time in the incubating means 200 to maintain the environment about said individual cell over time in a desired condition (page 13, lines 18 and 19). The apparatus comprises means 202 (page 12, line 22 through page 13, line 6; page 13, lines 11-16; page 24, lines 15-24; page 27, line 21 through page 30, line 9, figure 1a, figure 4c, figure 6) for automatically determining the state of said individual cell of the plurality of cells over time in the incubating means 200 (page 12, lines 1-3). The determining means 202 is in communication with the incubating means 200, the determining means 202 includes a computer 42 for automatically determining the state of said individual cell of the plurality of cells over time (page 12, lines 25-27).

Independent Claim 80 pertains to an apparatus for incubating and determining the state of individual cells within a plurality of cells. The apparatus comprises means 200 (page 12, lines 5-21) for incubating the plurality of cells, the incubating means 200 is a dynamically controlled closed environment in which the cells are grown and remains closed while it is dynamically controlled, which is maintained in a desired condition and in which each individual cell of the plurality of cells can be individually examined over time while the environment is dynamically controlled and maintained in the desired condition (page 11, lines 22-26). The apparatus comprises a robotic means 230 (page 14, lines 4-7) including a robotic arm for automatically

dispensing and aspirating different material while said cell of the plurality of cells are disposed in the incubating means 200 (page 48, line 2 and line 19). The apparatus comprises means 216 (figure 1b, page 13, line 17 through page 14, line 7) for automatically controlling the environment about said individual cell over time within the plurality of cells in the incubating means 200 to maintain the environment about said individual cell over time within the plurality of cells in a desired condition (page 13, lines 18 and 19).

Independent Claim 114 pertains to an apparatus for culturing and analyzing cells. The apparatus comprises a biochamber 10 having a plurality of cell housing containers 206, 208 in which cells to be cultured may be introduced therein, the biochamber being a dynamically controlled closed system in which the cells are grown (page 11, lines 22-26; page 12, line 5), the biochamber having an environment controlling means 216 (figure 1b, page 13, line 17 through page 14, line 7) for dynamically controlling the closed environment of the biochamber (page 13, lines 18 and 19). The apparatus comprises a liquid handling system for providing exchange of media to the cells while the cells are in the biochamber, the liquid handling system in fluid communication with the plurality of cell housing containers in the biochamber (page 14, lines 4-10). The apparatus comprises an image recognition system for analyzing the state of each cell of the cells over time that are disposed in the plurality of cell housing containers in the biochamber, the image recognition system utilizing image recognition software (page 12, lines 22-25). The apparatus comprises a stage 18 for supporting the biochamber, the biochamber, liquid handling system and image recognition system being in movable registration with respect to one another whereby the liquid handling system and image recognition system can access different cell

housing containers (page 13, line 3; page 17, line 19; page 23, lines 26-29). The apparatus comprises a system controller capable of regulating interaction between the biochamber, liquid handling system, image recognition system and stage (page 15, lines 15-19).

Dependent Claim 47 has the limitation of the imaging means (page 17,lines 1-7) includes means (page 17, lines 1-7) for phase contrast imaging to identify the state of said individual cell over time.

Dependent Claim 48 has the limitation of the phase contrast imaging means (page 17, lines 1-7) compares images to each other serially to identify the state of the cells.

Dependent Claim 52 has the limitation of the determining means (page 12, line 22 through page 13, line 6; page 13, lines 11-16; page 24, lines 15-24; page 27, line 21 through page 30, line 9, figure 1a, figure 4c, figure 6) includes means (page 4, lines 8-10; page 23, lines 22-24; page 27, line 21 through page 30, line 9, figure 1a, figure 4c, figure 6) for determining a biological event in said individual cell.

Dependent Claim 53 has the limitation of the determining means (page 12, line 22 through page 13, line 6; page 13, lines 11-16; page 24, lines 15-24; page 27, line 21 through page 30, line 9, figure 1a, figure 4c, figure 6) includes means (page 32, line 30 through page 33, line 21) for determining when a cell has doubled.

Dependent Claim 54 has the limitation of the determining means (page 12, line 22 through page 13, line 6; page 13, lines 11-16; page 24, lines 15-24; page 27, line 21 through page 30, line 9, figure 1a, figure 4c, figure 6) includes means (page 43, line 24 through page 45, line 27) for determining what stage a cell is in with respect to doubling.

Dependent Claim 55 has the limitation of the determining means (page 12, line 22 through page 13, line 6; page 13, lines 11-16; page 24, lines 15-24; page 27, line 21 through page 30, line 9, figure 1a, figure 4c, figure 6) includes means (page 30, lines 3-9) for determining the stage of the cell based on a metabolic process the cell is experiencing.

Dependent Claim 58 has the limitation of the biochamber includes a first well in which a first cell is disposed and a second well in which a second cell is disposed, and including means (page 14, lines 3-10; page 27, lines 21-28) for controlling the division and differentiation of the first cell and the second cell while the cells are in the incubating means.

Dependent Claim 59 has the limitation of the controlling means (page 14, lines 3-10; page 27, lines 21-28) controls the division and differentiation of the first cell differently from the way it controls the division and differentiation of the second cell while the cells are in the incubating means.

Dependent Claim 61 has the limitation of the controlling means (page 14, lines 3-10; page 27, lines 21-28) includes means (page 51, lines 21-31) for limiting differentiation of the daughter cells of the first cell.

Dependent Claim 62 has the limitation of the identifying means 212 (page 12, line 23 through page 13, line 6) includes means (page 14, lines 5-10; page 16, lines 14-19) for assessing synergistic or antagonistic effects of different combinations of factors on the cells.

Dependent Claim 63 has the limitation of the identifying means 212 (page 12, line 23 through page 13, line 6) includes means (page 32, lines 16-29) for identifying kinetic data for rates of cell division and differentiation.

Dependent Claim 64 has the limitation of the controlling means (page 14, lines 3-10; page 27, lines 21-28) controls the cell with transcriptional regulators and regulators associated with adherence in cell differences based on time.

Dependent Claim 76 has the limitation of the controlling means (page 14, lines 3-10; page 27, lines 21-28) includes means (page 26, lines 19-21) for exchanging n media, where n is greater than or equal to 2, in the incubating means.

Dependent Claim 79 has the limitation of means (page 27, lines 21 through page 30, line 8; page 40, lines 24-32) for automatically testing for predetermined biological variables and engineered genes with respect to each cell.

Dependent Claim 86 has the limitation of the incubating means (page 12, lines 5-21) has wells which hold corresponding cells and wherein the robotic means (page 14, lines 4-7) includes a pipette which transfers media from individual cells to the determining means at predetermined intervals.

Dependent Claim 87 has the limitation of the robotic means (page 14, lines 4-7) dispenses 1 to 95 microliters of media.

Dependent Claim 88 has the limitation of a liquid handling system connected to the robotic means (page 14, lines 4-7) and means (page 26, lines 24-31) for cleaning of the liquid handling system with wash cycles.

Dependent Claim 92 has the limitation of the robotic means (page 14, lines 4-7) includes a probe which, when placed in a well, identifies how much fluid is in the well.

Dependent Claim 95 has the limitation of the determining means (page 12, line 22 through page 13, line 6; page 13, lines 11-16) analyzes tissue culture media in a well with either biochemical, immuno chemical, biological or chemical assays.

Dependent Claim 96 has the limitation of the imaging means (page 17, lines 1-7) uses pattern recognition to correlate a state of a cell with a particular metabolic process of the cell.

Dependent Claim 97 has the limitation of a determining means (page 12, line 22 through page 13, line 6; page 13, lines 11-16; page 24, lines 15-24; page 27, line 21 through page 30, line 9, figure 1a, figure 4c, figure 6) for automatically testing for production or degradation of proteins, simple or complex sugars, individual amino acids, individual member ions, individual molecules with respect to both physical presence and biological activity in the incubating means, said determining means connected with the incubating means, said determining means including a computer.

Dependent Claim 100 has the limitation of a determining means (page 12, line 22 through page 13, line 6; page 13, lines 11-16; page 24, lines 15-24; page 27, line 21 through page 30, line 9, figure 1a, figure 4c, figure 6) for obtaining kinetic data for the rates of cell division differentiation, said determining means connected to the incubating means (page 12, lines 5-21).

Dependent Claim 103 has the limitation of the imaging means (page 17, lines 1-7) recognizes when a cell doubles in the incubating means by pattern recognition.

Dependent Claim 104 has the limitation of the determining means (page 12, line 22 through page 13, line 6; page 13, lines 11-16; page 24, lines 15-24; page 27, line 21 through page

30, line 9, figure 1a, figure 4c, figure 6) includes a plurality of dyes, each dye associated with a different cell surface marker, to identify cell surface markers on a cell.

VI. Grounds of Rejection to Be Reviewed on Appeal

1. The Examiner has rejected Claims 1, 47-64, 70, 74-81, 86-97, 99, 100, 103, 104 and 114-127 under 35 U.S.C. 103(a) as being unpatentable over Bisconte in view of Price.

VII. Argument

1. The Examiner has rejected Claims 1, 47-64, 70, 74-81, 86-97, 99, 100, 103, 104 and 114-127 under 35 U.S.C. 103(a) as being unpatentable over Bisconte in view of Price.

Claims 1, 52, 53, 94, 124 and 125

Appellants respectfully traverse this rejection.

Neither Bisconte nor Price, separately or in combination, teach or suggest a dynamically closed controlled environment in which cells are grown and in which each individual cell of a plurality of cells can be individually examined over time, as found in Claim 1 of Appellants.

Neither Bisconte nor Price, separately or in combination, teach or suggest means for automatically determining the state of an individual cell over time disposed in an incubating means.

Bisconte discloses an automatic device for the analysis and cloning of cellular cultures as well as for bacteriological analysis. Bisconte teaches that a plurality of cassettes 11 may be provided, each comprising its own plate 4, so as to facilitate storage particularly in a separate incubator (emphasis added), and so as to introduce into the first compartment 38, through the isothermal door 8 for closing the front face of enclosure 1, only the cassette corresponding to the

predetermined experimental protocol or the desired cassette. See column 7, lines 4-11 of Bisconte.

Bisconte teaches an enclosure 1 with isolating walls is divided into two compartments. There is compartment 3a which contains plate 4 of a cassette, the motor unit 5, a microscope observation device 6 and an aspiration/injection device. Compartment 3b completely surrounds the compartment 3a, except at the level of the access door 8 formed in the front face of the enclosure 1. These compartments are separated by a metal wall 9 made from steel or aluminum. Forced air flow is established between the two compartments. Flow of sterile and hot air passes through orifices in the bottom of compartment 3a. Plate 4 is made from a transparent material of good optical quality. Plate 4 may contain an external row of 16 microwells or 48 microwells depending on their diameter. Plate 4 is provided with a central opening for access to the aspirations/injection device in a discharge well 10 fixed to the lower wall of the first compartment 3a. The plate is disposed inside the cassette 11 square in shape which comprises a central circular recess 12 for housing plate 4. See column 6, lines 4-36. It is in compartment 3a that plate 4 is inserted for the desired experimental protocol to be performed. As mentioned above, and is clear from the text and figure 4, compartment 3a is not built for storage let alone a "dynamically controlled closed environment in which the cells are grown." Compartment 3a is just what Bisconte teaches it is, a receiving zone to insert a subject plate to perform the experimental protocols on the plate, and then for the plate to be removed and incubated in a separate location.

Plate 4 has a central opening for access to the aspirations/injection device in a discharge well 10 fixed to the lower wall of the first compartment 3a. A rotational drive for plate 4 is obtained by friction of the drive roller 14 and groove 13. See column 6, lines 33-55. Cassette 11 is provided with a transparent lid 16 fitted to the central opening in plate 44 to allow access of the aspiration/injection device into the discharge well 10. The lid 16 is provided with a radial window 17 for access of this aspiration/injection device into the microwells formed in plate 4 and aligned radially. See column 6, lines 65-68. Bisconte teaches it is sometimes necessary to vary the height of plate 4, for placing the needle 23 of the aspiration device 7 in contact with the cells 24 adhering to the bottom of the marker well 25 or for perfecting the optical focusing knowing that the microscope device is fixed and preset. See column 7, lines 29-44. For obtaining the horizontal movement of a plate 4, the stepper motor 30 is caused to act on a gear projecting from the motor unit 5 and acting in its turn on a rack 18 fixed to the lower wall of housing 19. See column 7, lines 54-60. Bisconte teaches that the motor unit 5 allows for different types of sweeps of the microwells 25, such as a continuous plot with low magnification, a continuous plot with high magnification or a sweep following any zigzag plot. Column 8, lines 1-5. Continuous sweeps allow for densitimetric profiles to be obtained while zig zag sweeps allow for random preprogrammed fields more corresponding to individual locations. See column 8, line 6-10.

Bisconte teaches a single lens/condenser pair is required. Lens 33 is placed in alignment with a condenser 34. The arrival of light into the condensers is provided by an optical fiber system 38. Pairs of lenses/condensers operate alternatively when the observation is to be made

with low magnification lens 33. An external prism sends a light beam onto the corresponding optical fiber. On leaving lens 33, the image is reflected by a mirror to the television camera placed either in compartment 3b or outside while extending the light guide G. In passing, the light rays pass through the mirror 42. See column 8, lines 25-45.

Bisconte teaches that the small volume of the compartment 3a provides automatic and constant humification by evaporation of the cellular medium contained in the microwell 25. The aspiration/injection device 7 is disposed in a vertical housing 45 formed in the upper wall of the first compartment 3a and cooperates with a device 46 for adjusting the height of nozzle 47. See column 9, lines 1-19. Aspiration takes place by retraction of piston 49 which sucks the membrane 50 through space 51. The depression thus created by membrane 50 is transmitted to space 52 and sucks up the liquid contained in the microwell 25. When the discharge well 10 is formed in the lower wall of compartment 3a, a cassette 11 is moved horizontally for aligning the central opening in plate 4 with nozzle 47 and well 10. The device 46 is then brought to a low position and collar 48 is applied against the upper surface of well 10 for providing ceiling. Piston 49 is then pushed back for driving out the liquid contained in 52. See column 9, lines 49-66.

Bisconte teaches that the main applications of the automatic device that is taught relate to cloning cellular cultures and the analysis of bacteria. In regard to cloning, the plate 4 is disposed in cassette 11 after a single microwell 25 has been seeded. From the identification of the colonies of cells, subcultures are formed and the other microwells of the plate are progressively

supplied by means of the aspiration/injection device. In regard to the analysis of materials, measurements are able to be taken at very close intervals of the cellular kinetics (imaging analysis). For analysis of bacteria, it occurs by colorimetric reactions. See column 10, lines 49-60.

It should be noted, that there is no discussion, nor teaching of any capability of tracking over time an individual cell in a group of cells in a dynamically controlled closed environment, as found in the claimed invention. All the teachings of Bisconte are directed to basically analysis and cloning of cellular cultures and for bacteriological analysis. See abstract. Accordingly, Bisconte does not teach or suggest the claimed invention of Appellants.

Moreover, it should be stressed that Bisconte teaches an aspiration/injection device to introduce or remove media to the colony of cells. There is no teaching to do any type of analysis on the removed media to determine the state of any cells. Only imaging is taught to be used to study the cell kinetics. See column 10, lines 56-60. No chemical analysis of the aspirated media whatsoever is taught or suggested by Bisconte.

Furthermore, from the above description, it is evident the context of Bisconte is a device that studies by imaging only colonies of cells in cartridges that are introduced into the device from a remote location where the colonies are incubated. The cartridge has a compartment that has automatic and constant humidification from the media in the wells and is large enough for an

aspiration device to fit through a central opening in the device. Through this central opening, humidification is also provided to the compartment 3a.

The Examiner, recognizing that Bisconte does not teach or suggest the claimed invention, cites Price in combination with Bisconte to arrive at appellants' claimed invention.

Referring to Price, in pertinent part, Price teaches to use short working distance objectives for image cytometry. Price teaches short working distance objectives require the use of a thin chamber. Price teaches that to control humidity and condensation on the microscope objectives, a closed static chamber is required as well as for sterility to be maintained while on the microscope stage. See column 23, lines 15, 16 and 19-26. To meet all these requirements, Price teaches the cell culture chamber design consists of a glass slide and coverslip of equal rectangular dimensions held 250 μM apart by a retainer made of Teflon. This retainer may contain access ports for the input and output of medium having the cells for study and the placement of a thermistor type temperature probe. Upper and lower aluminum rectangular frames hold the glass pieces of the Teflon retainer with enough pressure to create a seal. A thin film of vacuum grease may be applied between the Teflon and glass pieces if necessary. All medium infusion will be through the Teflon retainer and will contact only the glass once inside the chamber to avoid metallic ion toxicity. Temperature is controlled by use of a probe in direct contact with the control culture medium and a heating element in the baseplate of the stage. The design allows for assembly prior to autoclaving to minimize the kind of handling that compromises sterility. Cells are introduced by infusion and infusion is stopped long enough for

cell attachment. This design will simplify handling and facilitate multi-day microscope stage culturing. See column 23, lines 26-44 of Price.

It must be stressed that the placement and incubation of the cells on the slide in the chamber does not occur at the microscope device 100 that performs the analysis. The placement and incubation of the cells in the slide in the chamber occurs at a remote and separate location. Only when the chamber formation process is complete is the chamber manually carried to the microscope by a person and placed under the objective.

Moreover, it must be stressed that incubation of the cells also occurs of a remote and separate location. Examples that Price teaches are that incubation and growth last 5 to 8 days. See column 24, line 27. As Price teaches, the chamber is designed for multi-day microscope stage handling. See column 23, lines 44 and 45.

From the aforementioned description, it is clear that Price teaches a very thin glass chamber (250 μm thick) that is moved from another location to the microscope for scanning cytometry and then removed and put back at the other location for incubation by a person (since there is no mechanism taught by Price to mechanically move) to its storage location remote and apart from the microscope. It is also clear from the above, there is no teaching or suggestion that the environment of the chamber taught by Price is in any way dynamically controlled while "each individual cell of the plurality of cells is individually examined over time while the environment is dynamically controlled and maintained in the desired condition," as found in claim 1. Any

analysis of the cells is only accomplished by imaging. Any type of chemical analysis of the media aspirated from around the cell is not taught, suggested or capable.

Furthermore, Price teaches that the retainer may contain access ports for the input and output of medium at another location, but does not teach anywhere the use of "a robotic arm for dispensing and aspirating different material to each cell of the plurality of cells while the cells are disposed in the dynamically closed environment in the biochamber".

Thus, to summarize and reiterate, Price requires a very exact, very specific chamber design so the cytometry can be performed. The chamber that holds the cells must be very thin, and the statically closed so humidity and condensation do not interface with short working distance microscope objectives, and stability is maintained while on the stage. The chamber with the cells is also formed and incubated at a remote location to the microscope and carried to and removed from the microscope manually by a person. This is the context of Price.

It is the Examiner's position, as stated on the continuation sheet of the Advisory Action, that the reference of Bisconte discloses the use of an incubation chamber and optical interrogation using a microscope and camera imaging. In view of the disclosure of the reference of Price, one of ordinary skill in the art would have readily recognized that the system of Bisconte would be capable of performing other cell culture protocols, such as that disclosed by the reference of Price. "Modification of the system of Bisconte would merely (emphasis added) involve reprogramming the system components such that the cell scanning cytometry of Price

can be performed using image analysis and culture control." Appellants respectfully strongly traverse this conclusion by the Examiner.

It is respectfully submitted that the applied art of record does not arrive at appellants' claimed invention for several reasons dictated by patent law.

Patent law requires there be a teaching or suggestion in the applied art of record to arrive at the limitations of appellants" claimed invention. KSR International Co. v. TeleFlex, Inc., 550 U.S. 398 (2007). In Claim 1, there is the limitation of "determining means." This limitation is defined by 35 USC 112, paragraph 6 and requires that, simply speaking, the determining means utilizes both imaging and biochemistry to determine the state of a cell over time. For instance, the imaging utilizes a camera (page 13, lines 11 and 12) and the biochemistry utilizes a protein/nutrient analysis system (page 27, lines 23 and 24). The applied art of record is completely silent regarding the use of biochemistry to determine the state of the cell. 35 U.S.C. 112, paragraph 6 limits the definition or scope of the means language to that found in the specification and equivalents thereto. Warner-Jenkinson Co., Inc. v. Hilton Davis Chemical Co., 520 U.S. 17, 41 USPQ2d 1865 (1997). The means does not have any interpretation as is the Examiner's position.

Bisconte has to do only with cultures of cells and is silent regarding any type of control of any one cell relative to any other single cell. The Examiner has only cited Price for the purposes of reprogramming the optical aspects of Bisconte. Price does not teach or suggest anything at all

about control over individual cells, just imaging. As explained above, while Bisconte teaches the structure of the aspiration/injection device, it only is used to introduce media in or to take media out of the plate. Bisconte does not teach or suggest to do any type of analysis on the media to determine the state of the cell.

To reiterate and stress, neither Bisconte, nor Price teach or suggest the limitation of using biochemistry of the determining means. For this reason alone, Claim 1 is patentable over the applied art of record.

Moreover, the Examiner's rejection based on combining the teachings of Bisconte with the teachings of Price ignores the context in which each of these teachings are found. Patent law requires that the context of the teachings the Examiner relies upon cannot be taken out of the context in which they are found.

The Examiner cannot take the teachings of Price out of the context in which they are found, yet that is exactly what the Examiner is doing when the Examiner states that modification of the system of Bisconte would merely involve reprogramming the system components such that the cell scanning cytometry of Price can be performed using image analysis and culture control. As explained above, the teachings of Price are only applicable to its context. The teachings of Price to be able to track an individual cell over time requires cytometry which in turn requires a very thin, 250 μm thick chamber, that is statically maintained without humidity to interfere with the objectives. This is what Price specifically teaches is necessary to be able to perform the

analysis over time of an individual cell. Furthermore Price explains and teaches in great detail the efforts that must be taken to ensure the analysis can be performed. These teachings, in other words, the context of Price cannot be ignored. That is what is meant when the law requires the teachings cannot be taken out of context in which they are found. Quite simply, this statement by the Examiner that the system of Bisconte would merely involve reprogramming the system components such that the cell scanning cytometry of Price can be performed using image analysis and culture control ignores all of these requirements that Price teaches are critical. It also ignores that the system taught by Bisconte does not have the capability of tracking an individual cell over time.

Mere reprogramming does not solve the problem, as applicable to Price, of automatic and constant humidification by evaporation of the cellular medium contained in the microcells of Bisconte that would interfere with the objective lenses for cytometry.

Mere reprogramming does not solve the problem of the cassette being much larger than the 250 μm thickness of the chamber required by Price for cytometry.

Mere reprogramming does not solve the problem of the presence of a port in the top of the cassette required for aspiration of the microwells in Bisconte that would interfere with the closed static 250 μm thick chamber of Price.

All of this follows since the system taught by Bisconte is designed to study colonies of cells at a time. The study of colonies of cells at a time do not require the detailed studying that and individual cell over time requires. Colonies of cells are much larger than individual cells, so requirements are not as stringent to study colonies of cells. On the contrary, the study of colonies of cells requires a container such as a cassette taught by Bisconte, while the study of individual cells requires a different type of container that allows the individual cell to be identified over time. Appellants have discovered how to do this in a dynamically controlled environment in which the cells are incubated. The resultant advantage is that many cells can be analyzed over time in the very location they are growing under a controlled environment. There is no need to have to carry cells or even colonies of cells from a separate location with the attendant waste of time and risk of contamination, as is the case with the applied art of record.

The Examiner must take the prior art patents as a whole, and not take the teachings therein out of context and give the teachings meanings they would not have had to one skilled in the art having no knowledge of appellant's invention, or to anyone else who can read the specification with understanding. In re Wright, 9 U.S.P.Q. 1649 (Fed. Cir. 1989); Smithkline Diagnostics, Inc. v. Helena Laboratories Corp., 8 U.S.P.Q.2d 1468, 1475 (CAFC 1988). Bisconte analyzes cell cultures, not individual cells over time contrary to appellants' claimed invention; Bisconte incubates and grows the cell cultures in a remote location and then inserts a cassette with the cell cultures into the analyzing device, contrary to appellants' claimed invention. Bisconte examines the cell cultures in a static environment inside the cassette, contrary to appellants' claimed invention. Similarly, Price incubates the individual cells in a remote location

and then inserts the chamber with the cells before the microscope objective, contrary to appellants' claimed invention. Price examines the individual cells in a static environment inside the chamber, contrary to appellants' claimed invention.

There must be some teaching or suggestion in the applied art of record, or arising from the applied art of record to apply the teachings in the applied art of record the Examiner relies upon to arrive at appellants' claimed invention, and here, there is none. KSR International Co., supra.

Bisconte teaches to analyze cell cultures, found in a cassette by inserting the cassette into a device. Bisconte has no interest in analyzing individual cells over time at all. In fact, Bisconte is specifically interested in the overall effects on the entire cell colony over time.

Price teaches to perform cytometry on individual cells. Price has no interest in analyzing cell cultures in any way, and to even consider Price to do so, would eliminate the entire purpose of Price and make cytometry, the key of Price, useless for its intended purpose. Cytometry could not be performed on cell cultures in the cassette holding the cell cultures taught by Bisconte.

The Examiner cannot ignore that Price teaches a very small glass chamber that is moved from another location to the microscope for analysis. This glass chamber is not dynamically controlled at all and is not designed for a robotic arm to dispense or aspirate material into or from it. At minimum, it would require one skilled in the art to have to experiment, research and

develop a new design to allow for these features. This does not even speak yet to somehow making the new design work with the system of Bisconte. This only supports a finding of nonobviousness.

In addition, as mentioned above, there must be some teaching or suggestion to combine the teachings of these two references, and there is none. There is no teaching or suggestion and Bisconte of the needs to individually examine over time each individual cell of a plurality of cells, as found in Claim 1 of Appellants. In fact, as has been already stated, Bisconte is only concerned with cell cultures, not at all with individual cells. Price provides no teaching or suggestion, or even the need, of examining over time each individual cell of a plurality of cells in a dynamically controlled environment.

As the court stated in Innogenetics, N.V. v. Abbott Laboratories, 512 F.3d 1363 (Fed. Cir. 2008)

> We must still be careful not to allow hindsight reconstruction of references to reach the claimed invention without any explanation as to how or why the references would be combined to produce the claimed invention.

Even the problems that Bisconte and Price solve are distinct from each other and from Appellants' claimed invention. Appellants' claimed invention is directed to examining each cell of a plurality of cells individually over time in a dynamically controlled closed environment. Bisconte is directed to analyzing and cloning cellular cultures. Price is directed to increasing the

efficiency of scanning cytometry. Accordingly, since the problems that the two references solve are distinct from each other and from the problem that Appellants' claimed invention cells, there is no basis or support from their respective problems to cause one skilled in the art to arrive at Appellants' claimed invention by combining the teachings of Price and Bisconte. For this reason, the combination of Price and Bisconte, under patent law, do not arrive at Appellants' claimed invention.

It is respectfully submitted the Examiner is using the limitations of Appellants' claims as a roadmap to find the limitations in various disparate references, and supposedly having found them, concluding that Appellants' claimed invention is arrived at. This is the use of hindsight, which is contrary to patent law. It is only this hindsight, that provides any explanation as to why Price and Bisconte would be combined.

It should also be noted that the chamber of Price and the plate of Bisconte are in conflict. The chamber of Price is taught to be closed and sealed and very thin so cytometry can be successfully performed. In contrast, the plate of Bisconte is very thick an open to hold the wells and aspirate/dispense from or into the wells. Based on the teachings of Price, it is submitted such a plate design of Bisconte would not allow for successful cytometry, so the tracking of a cell over time could not occur. This follows because Bisconte is concerned only with cell cultures. The teaching of a thin sealed chamber by Price thus teaches away from a thick open plate of Bisconte, and for this reason alone, one skilled in the art would not look or consider to combine the teachings of Price with the teachings of Bisconte.

Moreover, in Smithkline Diagnostics, Inc., supra, the court held:

> Helena cannot pick and choose among the individual elements of assorted prior art references to recreate the claimed invention. See, e.g. Azko N.V. v. United States Int'l Trade Comm'n, 808 F.2d 1471, 1481, 1 U.S.P.Q.2d 1241, 1246 (Fed. Cir. 1986), cert, denied, 107 S.Ct. 2490 (1987). Helena has the burden to show some teaching or suggestion in the references to support their use in the particular claimed combination. Uniroyal, Inc., 837 F.2d at 1051, 5 U.S.P.Q.2d at 1438-39. A holding that combination claims are invalid based merely upon finding similar elements in separate prior art patents would be "contrary to statute and would defeat the congressional purpose in enacting Title 35." Panduit Corp., 810 F.2d at 1577, 1 U.S.P.Q.2d at 1605.

The Examiner is picking and choosing appellant's claimed elements and supposedly having found the various claimed elements, concludes appellant's claimed invention is arrived at, without any acknowledgment of the context in which the elements are found.

It is respectfully submitted, that the Examiner is using hindsight to attempt to arrive at appellants' claimed invention. The Examiner is using appellants' claims as a roadmap to find the different limitations in the different references, and having supposedly found them, concludes that appellants' claimed invention is arrived at. This is not patent law. Ruiz v. A. B. Chance Co., 357 F.3d 1270, 69 USPQ2d 1686 (Fed. Cir. 2004). Except for hindsight, there is no reason for one skilled in the art to combine the applied art of record. They basically have nothing to do with each other.

Furthermore, Bisconte does not teach or suggest an incubating means which is dynamically controlled closed environment in which the cells are grown and in which each individual cell of the plurality of cells can be individually examined over time while the environment is dynamically controlled and maintained in the desired condition, as found in Claim 1. On the continuation sheet of the advisory action dated September 23, 2009, the examiner takes the position that "Bisconte discloses a dynamically control closed environment in which cells are grown. Specifically the reference discloses a closed environment (3A and/or 3B) for controlling the conditions of the cells which includes allowing the cells to be ground (see column 2, lines 29-33 and lines 43-48). The fact that the cassettes of Bisconte can also be cultured in a separate incubator as argued by Appellants is immaterial since the conditions within the chambers (3A and/or 3B) can also be controlled when performing a predetermined experimental protocol with a desired set". Appellants respectfully strongly traverse this rejection.

In relevant part, all that Bisconte really teaches is a sterile cassette that has a lid in it so the aspiration device 7 can be inserted through the lid and communicate with the plate 4. As Bisconte teaches, the plate is disposed inside a cassette 11, made from metal, square in shape with rounded angles. See column 6, lines 33-35. Cassette 11 is provided with a transparent lid 16 of good optical quality, fitted to said central opening in plate 4 for access of the aspiration/injection device. See column 6, line 65-68. The humidity from evaporation of the media in the wells escapes the cassette and humidifies the compartment 3a. See column 9, lines 3-6. Those are the specific teachings that describe the cassette 11 of Bisconte. Thus it is clear, there is absolutely no dynamic environment in which each individual cell of the plurality of cells

can be individually examined over time while the environment is dynamically controlled and maintained in the desired condition. At best, the environmental conditions are static. There is no teaching or suggestion of any type of ports of any other type of capability to change the environment inside the cassette in which the cells are located. It is only the lid that provides access to the cells for the aspiration/injection device, but that has nothing at all to do with the environment.

Even the compartment 3A and 3B that the examiner refers to does not have a dynamically controlled environment. Bisconte teaches that a forced airflow is established between the two compartments 3A and 3B and a filter is entered for retaining particles and limiting contamination. See column 6, lines 19-22. The flow of sterile and hot air thus obtained passes through orifices which may be formed in the bottom of compartment 3A. That is it! That is all that Bisconte specifically teaches about the environment. The flow of sterile and hot air is not dynamic. The flow of sterile and hot air is outside of the cassette and flows from compartment 3B to compartment 3A.

The language that the Examiner refers to for support that Bisconte teaches that the cells can be individually examined over time while the environment is dynamically controlled and maintained in the desired condition is found in the summary of the invention section of Bisconte. It is respectfully submitted the Examiner is trying to apply an interpretation to the very general language in the summary to arrive at appellants' claimed invention. In column 2, lines 29-33, Bisconte simply teaches another aim of the invention is to allow the environmental conditions of

the cells, including the nutritive media to be made dependent, by means of software, on parameters measured frequently or even continuously. From this general language, and then a review of the "Description of the Invention" section of Bisconte, the only corresponding language that conforms to the general language in the summary, is in regard to the aspiration/injection device. However, this only has to do with the medium in which the cells are actually in, and not the environment as defined by appellants'. This can be seen by the fact that appellants' claimed invention has an incubating means and also an automatically determining means. As part of the incubating means, there is an environment controlling means.

As the language in the claims of appellants' is a means plus function language, 35 USC 112 paragraph 6 dictates that to determine the environment controlling means, one must review the specification to understand the scope of this limitation. The scope is not limited to any type of interpretation whatsoever, but specifically to that identified inside the specification. Warner-Jenkinson Co., Inc., supra. In regard to the environmental controlling means of appellants', it covers not only the material or medium in which the cell is found, but also the surrounding environment that covers the cell. This can be seen from page 13, lines 17-31 of appellants' specification where the in environment controlling mechanism 216 covers temperature, media pH and pressure, all of which are dynamically controlled. As explained above, the specific teachings of Bisconte do not provide for any dynamic control of the area outside of the medium in which the cell is disposed.

In regard to lines 43-48 of column 2 of Bisconte, it simply teaches that there is an enclosure with isolating walls, providing homeothermic conditions and certain environmental conditions, particularly in terms of geometry, percentage of CO2 and/or others, inside this enclosure, which is divided into two compartments. Again, this citation is part of the summary of the invention, and a review of the more specific enabling portion of Bisconte found under the Description of the Invention section reveals there are no teachings to explain specifically what this language means in the Summary section, let alone how to carry it out. In addition, this language in the Summary is referring to the enclosures 3A and 3B, but as explained above, the cassette isolates the cells in the cassette from the compartments. Accordingly, it is respectfully submitted there is no means for incubating the plurality of cells which includes an environment controlling means for dynamically controlling the closed environment of the incubating means. The Examiner does not cite Price teaching a dynamically control closed environment. For this additional reason, Claim 1 is patentable over the applied art of record.

Claims 52, 53, 94, 124 and 125 are dependent to parent Claim 1 and are patentable for the reasons Claim 1 is patentable.

Claim 47

Claim 47 is dependent to Claim 1 and is patentable for the reasons Claim 1 is patentable. Claim 47 has the limitation that the imaging means includes means for phrase contrast imaging to identify the state of said individual cells over time. It is respectfully submitted the applied art

of record does not teach or suggest this limitation. Accordingly, Claim 47 is additionally patentable for this reason.

Claim 48

Claim 48 is dependent to Claim 1 and is patentable for the reasons Claim 1 is patentable. Claim 48 has the limitation that the phase contrast imaging means compares images to each other serially to identify the state of the cells. It is respectfully submitted the applied art of record does not teach or suggest this limitation. Claim 47 is additionally patentable over the applied art of record for this reason.

Claim 49

Claim 49 is dependent to Claim 1 and is patentable for the reasons Claim 1 is patentable. Claim 49 has the limitation that the imaging means acquires two successive fluorescent images of each cell and compares them to each other serially to identify the state of each cell. It is respectfully submitted the applied art of record does not teach or suggest this limitation. Claim 49 is additionally patentable for this reason.

Claim 50

Claim 50 is dependent to Claim 1 and is patentable for the reasons Claim 1 is patentable. Claim 50 has the limitation that the imaging means includes antibody type labels with different colors of dies for use to detect the presence of cell surface markers. It is respectfully submitted the applied art of record does not teach or suggest this limitation. For this reason, Claim 50 is additionally patentable.

Claim 54

Claim 54 is dependent to Claim 1 and is patentable for the reasons Claim 1 is patentable. Claim 54 has the limitation of means for determining what stage a cell is in with respect to double in. It is respectfully submitted the applied art of record does not teach or suggest this limitation. Claim 54 is additionally patentable for this reason.

Claim 55

Claim 55 is dependent to Claim 1 and is patentable for the reasons Claim 1 is patentable. Claim 55 has the limitation of means for determining the status of the cell based on a metabolic process the cell is experiencing. It is respectfully submitted the applied art of record does not teach or suggest this limitation. Claim 55 is additionally patentable for this reason.

Claim 56

Claim 56 is dependent to Claim 1 and is patentable for the reasons Claim 1 is patentable. Claim 56 has the limitation that the determining means identifies the production or degration of proteins, simple or complex sugars, individual amino acids, individual ions, individual molecules with respect to both physical presence and biological activity of the cell. It is respectfully submitted the applied art of record does not teach or suggest this limitation. Claim 56 is additionally patentable for this reason.

Claim 96

Claim 96 is dependent to Claim 1 and is patentable for the reasons Claim 1 is patentable. Claim 96 has the limitation that the imaging means uses pattern recognition to correlate a state of a cell with a particular metabolic process of the cell. It is respectfully submitted the applied art of record does not teach or suggest this limitation. Claim 96 is additionally patentable for this reason.

Claim 103

Claim 103 is dependent to Claim 1 and is patentable for the reasons Claim 1 is patentable. Claim 103 has the limitation the imaging means recognizes when a cell doubles in the incubating means by pattern recognition. It is respectfully submitted the applied art of record does not teach or suggest this limitation. Claim 103 is additionally patentable for this reason.

Claim 104

Claim 104 is dependent to Claim 1 and is patentable for the reasons Claim 1 is patentable. Claim 104 has the limitation that the determining means includes a plurality of dyes, each dye associated with a different cell surface marker, to identify cell surface markers on a cell. It is respectfully submitted the applied art of record does not teach or suggest this limitation. Claim 104 is additionally patentable for this reason.

Claims 51 and 126

Claim 51 is patentable for the reasons Claim 1 is patentable. Moreover, Claim 51 has the limitation of means for automatically determining the state of said individual cell of the plurality of cells in real time. The applied art of record is silent in regard to this limitation. Claim 51 is additionally patentable for this reason. Claim 126 is dependent to Claim 51 and is patentable for the reasons Claim 51 is patentable.

Claims 57 and 127

Claim 57 is patentable for the reasons Claim 1 is patentable in regard to the use of imaging and the environment controlling means. Claim 127 is dependent to parent Claim 57 and is patentable for the reasons Claim 57 is patentable.

Claim 58

Claim 58 is dependent to Claim 57 and is patentable for the reasons Claim 57 is patentable. Claim 58 has the limitation of the means for controlling the division and differentiation of the first cell and the second cell while the cells are in the incubating means. It is respectfully submitted the applied art of record does not teach or suggest this limitation. Again, Bisconte has to do only with cultures of cells and is silent regarding any type of control of any one cell relative to any other single cell. The examiner has only cited Price for the purposes of reprogramming the optical aspects of Bisconte. Price does not teach or suggest anything at all about control over individual cells, just imaging. Accordingly, Claim 58 is additionally patentable over the applied art of record for this reason.

Claim 59

Claim 59 is dependent to Claim 57 and is patentable for the reasons Claim 57 is patentable. Claim 59 has the limitation of the controlling means controls the division and differentiation of the first cell differently from the way it controls the division and differentiation of the second cell or the cells are in the incubating means. It is respectfully submitted the applied art of record does not teach or suggest this limitation. Claim 59 is additionally patentable for this reason.

Claim 60

Claim 60 is dependent to Claim 57 and is patentable for the reasons Claim 57 is patentable. Claim 60 has the limitation that the first cell is a different type of cell than the second cell. It is respectfully submitted the applied art of record does not teach or suggest this limitation. Claim 60 is additionally patentable over the applied art of record for this reason.

Claim 61

Claim 61 is dependent to Claim 57 and is patentable for the reasons Claim 57 is patentable. Claim 61 has the limitation that the controlling means includes means for limiting differentiation of the daughter cells of the first cell. It is respectfully submitted the applied art of record does not teach or suggest this limitation. Claim 61 is additionally patentable for this reason.

Claim 62

Claim 62 is dependent to Claim 57 and is patentable for the reasons Claim 57 is patentable. Claim 62 has the limitation that the identifying means includes means for assessing synergistic or antagonistic effects of different combinations of factors on the cells. It is respectfully submitted the applied art of record does not teach or suggest this limitation. Claim 62 is additionally patentable for this reason.

Claim 63

Claim 63 is dependent to Claim 57 and is patentable for the reasons Claim 57 is patentable. Claim 63 has a limitation that the identifying means includes means for identifying genetic data for rates of cell division and differentiation. It is respectfully submitted the applied art of record does not teach or suggest this limitation. Claim 63 is additionally patentable for this reason.

Claim 64

Claim 64 is dependent to Claim 57 and is patentable for the reasons Claim 57 is patentable. Claim 64 has the limitation that the controlling means controls the cell with transcriptional regulators and regulators associated with adherence in cell differences based on time. It is respectfully submitted the applied art of record does not teach us suggest this limitation. Claim 64 is additionally patentable for this reason.

Claim 70

Claim 70 is patentable for the reasons Claim 1 is patentable. Claim 70 also has the limitation of means for individually controlling automatically the division and differentiation of the first cell and at least the second cell amongst the plurality of cells while the cells are in the incubating means, said controlling means automatically controls the division and differentiation

of the first cell differently from the way controls the division and differentiation of the second cell amongst the plurality of cells on the cells are in the incubating means. It is respectfully submitted the applied art of record does not teach or suggest this limitation. Bisconte has to do only with cultures of cells and is silent regarding any type of control of any one cell relative to any other single cell. The examiner has only cited Price for the purposes of reprogramming the optical aspects of Bisconte. Price does not teach or suggest anything at all about control over individual cells, just imaging. Accordingly, Claim 70 is additionally patentable over the applied art of record for this reason.

Claim 74

Claim 74 is patentable over the applied art of record for the reasons Claim 1 is patentable. Claim 74 also has the limitation of a means for automatically determining a desired state of the stem cell within the plurality of cells over time in the incubating means and means for automatically introducing quiescence media to the stem cell within the plurality of cells in the incubating means when the stem cell is in the desired state to inhibit the proliferation or selected differentiation of the stem cell in the incubating means. Claim 74 is additionally patentable over the applied art of record for the reasons Claim 70 is additionally patentable over the applied art of record. Furthermore, the applied art of record does not teach or suggest anything at all about stem cells. For this additional reason, Claim 74 is patentable over the applied art of record.

Claims 75, 76 and 78

Claim 75 is patentable for the reasons Claim 1 is patentable. Claims 76 and 78 are dependent to parent Claim 75 and are patentable for the reasons Claim 75 is patentable.

Claim 77

Claim 77 is dependent to Claim 75 and is patentable for the reasons Claim 75 is patentable. Claim 77 has the limitation that the incubating means includes m wells, where m is greater than or equal to 2, and the cell is disposed in a first well of the m wells, and exchanging means exchanges n medias in the first well. It is respectfully submitted the applied art of record does not teach or suggest this limitation. Bisconte does not teach or suggest anything at all whatsoever in regard to an individual cell let alone exchanging n media in only one well with the one cell. Claim 77 is additionally patentable for this reason.

Claim 79

Claim 79 is dependent to Claim 75 and is patentable for the reasons Claim 75 is patentable. Claim 79 has the limitation of means for automatically testing for predetermined biological variables and engineered genes with respect to each cell. The applied art of record does not teach or suggest this limitation. Claim 79 is additionally patentable for this reason.

Claims 80, 87, 88, 90, 91, 93 and 99

Claim 80 is patentable for the reasons Claim 1 is patentable in regard to the use of the environment controlling means. Claims 87, 88, 90, 91, 93 and 99 are dependent to parent Claim 80 and are patentable for the reasons Claim 80 is patentable.

Claim 81

Claim 81 is dependent to Claim 80 and is patentable for the reasons Claim 80 is patentable. Claim 81 has the limitation of a supply of antigen and a supply of fluorochrome connected to the robotic means for antigen or fluorochrome can be dispensed to the cells in the incubating means. It is respectfully submitted the applied art of record does not teach or suggest this limitation. Claim 81 is patentable for this additional reason.

Claim 86

Claim 86 is dependent to Claim 80 and is patentable for the reasons Claim 80 is patentable. Claim 86 has the limitation that the robotic means includes the pipette transfers media from individual cells to the determining means at predetermined intervals. It is respectfully submitted the applied art of record does not teach or suggest this limitation. Claim 86 is additionally patentable for this reason.

Claim 89

Claim 89 is dependent to Claim 80 and is patentable for the reasons Claim 80 is patentable. Claim 89 has the limitation of P additional pipettes in communication with the wells, each pipette can either aspirate or dispense liquid to the wells, where P is an integer greater than or equal to 2. It is respectfully submitted the applied art of record does not teach or suggest this limitation. Bisconte teaches a single needle to aspirate or inject media into the cassette. Furthermore the cassette has only a single opening to accommodate just one pipette. Accordingly, Claim 89 is additionally patentable for this reason.

Claim 92

Claim 92 is dependent to Claim 89 and is patentable for the reasons Claim 89 is patentable. Claim 92 has the limitation that the robotic means includes a probe which, when placed in a well, identifies how much fluid is in the well. It is respectfully submitted the applied art of record does not teach or suggest this limitation. Claim 92 is additionally patentable for this reason.

Claim 95

Claim 95 is dependent to Claim 89 and is patentable for the reasons Claim 89 is patentable. Claim 95 has the limitation that the determining means analyzes tissue culture media in a well with either biochemical, immuno chemical, biological or chemical assays. It is

respectfully submitted the applied art of record does not teach or suggest this limitation. Claim 95 is additionally patentable for this reason.

Claim 97

Claim 97 is dependent to Claim 89 and is patentable for the reasons Claim 89 is patentable. Claim 97 has the limitation of a determining means for automatically testing for production or degradation of proteins, simple or complex sugars, individual amino acids, individual member ions, individual molecules with respect to both physical presence and biological activity in the incubating means. It is respectfully submitted the applied art of record does not teach or suggest this limitation. Claim 97 is additionally patentable for this reason.

Claim 100

Claim 100 is dependent to Claim 89 and is patentable for the reasons Claim 89 is patentable. Claim 100 has the limitation of a determining means for obtaining kinetic data for the rates of cell division and differentiation. It is respectfully submitted the applied art of record does not teach or suggest this limitation. Claim 100 is additionally patentable for this reason.

Claims 114, 115, 118, 120, 122 and 123

Claim 114 has the limitation that the biochamber being a dynamically controlled closed system in which the cells are grown, the biochamber having an environment controlling means for dynamically controlling the closed environment of the biochamber. For the reasons explained above in regard to Claim 1 and the environment controlling means, Claim 114 is patentable over the applied art of record.

Claim 114 also has the limitation of an image recognition system for analyzing the state of each cell of the cells over time that are disposed in the plurality of cell housing containers in the biochamber. For the reasons explained above in regard to Claim 1 as to why the applied art of record does not arrive at the limitation of analyzing the state of each cell of the cells over time that are disposed in the plurality of cell housing containers; which are in summary, because Bisconte does not teach or suggest the analysis of any individual cell of a plurality of cells over time, and the teachings of Price cannot be used to merely reprogram Bisconte, for this reason also, Claim 114 is patentable over the applied art of record. Claims 115, 118, 120, 122 and 123 are dependent to parent Claim 114 and are patentable for the reasons Claim 114 is patentable.

Claim 116

Claim 116 is dependent to Claim 114 and is patentable for the reasons Claim 114 is patentable. Claim 116 has a limitation that the derived images are processed by the image recognition software to determine cellular characteristics of the cells. It is respectfully submitted

the applied art of record does not teach or suggest this limitation. Claim 116 is additionally patentable for this reason.

Claim 117

Claim 117 is dependent to Claim 114 and is patentable for the reasons Claim 114 is patentable. Claim 117 has a limitation that upon determination a particular cellular characteristics of the cells, the system controller is prompted to actuate the liquid handling system to provide exchange of media to the cells. It is respectfully submitted the applied art of record does not teach or suggest this limitation. Claim 117 is additionally patentable for the reasons Claim 70 is additionally patentable over the applied art of record. Bisconte has nothing at all to do with the identification or imaging of individual cells and a plurality of cells. Furthermore Bisconte does not teach you just anything about actuating the aspiration/injection device in response to particular cellular characteristics. Price only teaches the image cytometry or imaging cells. Price does not teach or suggest to link the cellular characteristics of the cells to the actuation of a liquid handling system to provide exchange of media to the cells. Accordingly, Claim 117 is additionally patentable for this reason.

Claim 119

Claim 119 is dependent to Claim 114 and is patentable for the reasons Claim 114 is patentable. Claim 119 has the limitation that the liquid handling system further comprises a

plurality of pipettes for providing the exchange of media to the cells, the plurality of pipettes the movable along X, Y and Z dimensions with respect the plurality of cell housing containers. For the reasons that Claim 89 is additionally patentable over the applied art of record, Claim 119 is also additionally patentable over the applied art of record.

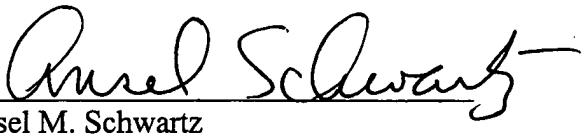
Claim 121

Claim 121 is dependent to Claim 114 and is patentable for the reasons Claim 114 is patentable. Claim 121 has the limitation that the image recognition system is capable determining varying cellular characteristics and the system controller regulates the biochamber and liquid handling system in response to the determined cellular characteristics. It is respectfully submitted that the applied art of record does not teach or suggest this limitation and is additionally patentable for the reasons Claim 117 is patentable over the applied art of record.

For all the aforesaid reasons, appellants' claims, as identified in each of the claims argued above, are not arrived at by the applied art of record.

Accordingly, reconsideration is requested and the reversal of the Examiner by the Honorable Board of Appeals is respectfully solicited.

Respectfully submitted,



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VIII. Claims Appendix

1. An apparatus for incubating and determining the state of individual cells within a plurality of cells comprising:

means for incubating the plurality of cells, the incubating means is a dynamically controlled closed environment in which the cells are grown and remains closed while it is dynamically controlled, which is maintained in a desired condition and in which each individual cell of the plurality of cells can be individually examined over time while the environment is dynamically controlled and maintained in the desired condition, the incubating means including an environment controlling means for dynamically controlling the closed environment of the incubating means; and

means for automatically determining the state of said individual cell of the plurality of cells over time disposed in the incubating means while the environment is dynamically controlled and maintained in the desired condition, said determining means in communication with the incubating means, said determining means includes a computer for automatically determining the state of said individual cell of the plurality of cells over time.

47. An apparatus as described in Claim 124 wherein the imaging means includes means for phase contrast imaging to identify the state of said individual cell over time.

48. An apparatus as described in Claim 47 wherein the phase contrast imaging means compares images to each other serially to identify the state of the cells.

49. An apparatus as described in Claim 124 wherein the imaging means acquires two successive fluorescent images of each cell and compares them to each other serially to identify the state of each cell.

50. An apparatus as described in Claim 124 wherein the imaging means includes antibody type labels with different colors of dyes for use to detect the presence of cell surface markers.

51. An apparatus for incubating and determining the state of individual cells within a plurality of cells comprising:

means for incubating the plurality of cells, the incubating means is a dynamically controlled closed environment in which the cells are grown and remains closed while it is dynamically controlled, which is maintained in a desired condition and in which each individual cell of the plurality of cells can be examined in real time over time while the environment is dynamically controlled and maintained in the desired condition, the incubating means including an environment controlling means for dynamically controlling the closed environment of the incubating means; and

means for automatically determining the state of said individual cell of the plurality of cells in real time over time disposed in the incubating means, said determining means in communication with the incubating means while the environment is dynamically controlled and maintained in the desired condition, said determining means including a computer for automatically determining the state of said individual cell of the plurality of cells in real time over time.

52. An apparatus as described in Claim 124 wherein the determining means includes means for determining a biological event in said individual cell.

53. An apparatus as described in Claim 52 wherein the determining means includes means for determining when a cell has doubled.

54. An apparatus as described in Claim 53 wherein the determining means includes means for determining what stage a cell is in with respect to doubling.

55. An apparatus as described in Claim 54 wherein the determining means includes means for determining the stage of the cell based on a metabolic process the cell is experiencing.

56. An apparatus as described in Claim 55 wherein the determining means identifies the production or degration of proteins, simple or complex sugars, individual amino acids, individual

ions, or individual molecules with respect to both physical presence and biological activity of the cell.

57. An apparatus for incubating and determining the state of individual cells within a plurality of cells comprising:

means for incubating the plurality of cells, the incubating means is a dynamically controlled closed environment in which the cells are grown and remains closed while it is dynamically controlled, which is maintained in a desired condition and in which each individual cell of the plurality of cells can be examined over time while the environment is dynamically controlled and maintained in the desired condition, the incubating means including an environment controlling means for dynamically controlling the closed environment of the incubating means; and

means for automatically tracking and identifying division and differentiation of said individual cell from the plurality of cells over time in the incubating means, said incubating means in communication with the tracking and identifying means, the tracking and identifying means including a computer for automatically tracking and identifying division and differentiation of said individual cell from the plurality of cells over time.

58. An apparatus as described in Claim 127 wherein the biochamber includes a first well in which a first cell is disposed and a second well in which a second cell is disposed, and

including means for controlling the division and differentiation of the first cell and the second cell while the cells are in the incubating means.

59. An apparatus as described in Claim 58 wherein the controlling means controls the division and differentiation of the first cell differently from the way it controls the division and differentiation of the second cell while the cells are in the incubating means.

60. An apparatus as described in Claim 59 wherein the first cell is a different type of cell then the second cell.

61. An apparatus as described in Claim 60 wherein the controlling means includes means for limiting differentiation of the daughter cells of the first cell.

62. An apparatus has described in Claim 61 wherein the identifying means includes means for assessing synergistic or antagonistic effects of different combinations of factors on the cells.

63. An apparatus as described in Claim 62 wherein the identifying means includes means for identifying kinetic data for rates of cell division and differentiation.

64. An apparatus as described in Claim 63 wherein the controlling means controls the cell with transcriptional regulators and regulators associated with adherence in cell differences based on time.

70. An apparatus for incubating and determining the state of individual cells within a plurality of cells comprising:

means for incubating a first cell and at least a second cell amongst the plurality of cells, the incubating means is a dynamically controlled closed environment in which the cells are grown and remains closed while it is dynamically controlled, which is maintained in a desired condition and in which the first cell and at least the second cell can be individually examined over time amongst the plurality of cells while the environment is dynamically controlled and maintained in the desired condition, the incubating means including an environment controlling means for dynamically controlling the closed environment of the incubating means;

means for individually controlling automatically the division and differentiation of the first cell and at least the second cell amongst the plurality of cells while the cells are in the incubating means, said controlling means automatically controls the division and differentiation of the first cell differently from the way it controls the division and differentiation of the second cell amongst the plurality of cells while the cells are in the incubating means, the controlling means in communication with the incubating means; and

means for individually tracking and identifying division and differentiation automatically of the first cell and at least the second cell amongst the plurality of cells over time in the incubating means, the tracking and identifying means in communication with the incubating means, the tracking and identifying means including a computer for individually tracking and identifying division and differentiation automatically of the first cell and at least the second cell amongst the plurality of cells over time.

74. An apparatus for incubating and determining the state of a stem cell within a plurality of cells comprising:

means for incubating the plurality of cells, the incubating means is a dynamically controlled closed environment in which the cells are grown and remains closed while it is dynamically controlled, which is maintained in a desired condition and in which each individual cell of the plurality of cells can be individually examined over time while the environment is dynamically controlled and maintained in the desired condition, the incubating means including an environment controlling means for dynamically controlling the closed environment of the incubating means;

means for automatically determining a desired state of the stem cell within the plurality of cells over time in the incubating means, the determining means connected to the incubating means, the determining means in communication with the incubating means, the determining

means including a computer for automatically determining a desired state of the stem cell within the plurality of cells over time; and

means for automatically introducing quiescence media to the stem cell within the plurality of cells in the incubating means when the stem cell is in the desired state to inhibit the proliferation or selected differentiation of the stem cell in the incubating means, said introducing means connected to the incubating means, the introducing means in communication with the incubating means.

75. An apparatus for incubating and determining the state of individual cells within a plurality of cells comprising:

means for incubating the plurality of cells, the incubating means is a dynamically controlled closed environment in which the cells are grown and remains closed while it is dynamically controlled, which is maintained in a desired condition and in which each individual cell of the plurality of cells can be individually examined over time while the environment is dynamically controlled and maintained in the desired condition, said incubating means having means for controlling the environment about said individual cell over time in the incubating means to maintain the environment about said individual cell over time in a desired condition; and

means for automatically determining the state of said individual cell of the plurality of cells over time in the incubating means, said determining means in communication with the incubating means, the determining means including a computer for automatically determining the state of said individual cell of the plurality of cells over time.

76. An apparatus as described in Claim 75 wherein the controlling means includes means for exchanging n media, where n is greater than or equal to 2, in the incubating means.

77. An apparatus as described in Claim 76 wherein the incubating means includes m wells, where m is greater than or equal to 2, and the cell is disposed in a first of the m wells, and the exchanging means exchanges n media in the first well.

78. An apparatus as described in Claim 76 wherein n equals 96.

79. An apparatus as described in Claim 75 including means for automatically testing for predetermined biological variables and engineered genes with respect to each cell.

80. An apparatus for incubating and determining the state of individual cells within a plurality of cells comprising:

means for incubating the plurality of cells, the incubating means is a dynamically controlled closed environment in which the cells are grown and remains closed while it is

dynamically controlled, which is maintained in a desired condition and in which each individual cell of the plurality of cells can be individually examined over time while the environment is dynamically controlled and maintained in the desired condition;

a robotic means including a robotic arm for automatically dispensing and aspirating different material while said cell of the plurality of cells are disposed in the incubating means; and

means for automatically controlling the environment about said individual cell over time within the plurality of cells in the incubating means to maintain the environment about said individual cell over time within the plurality of cells in a desired condition.

81. An apparatus as described in Claim 80 including a supply of antigen and a supply of fluorochrome connected to the robotic means so antigen or fluorochrome can be dispensed to the cells in the incubating means.

86. An apparatus as described in Claim 80 wherein the incubating means has wells which hold corresponding cells and wherein the robotic means includes a pipette which transfers media from individual cells to the determining means at predetermined intervals.

87. An apparatus as described in Claim 80 wherein the robotic means dispenses 1 to 95 microliters of media.

88. An apparatus as described in Claim 80 including a liquid handling system connected to the robotic means and means for cleaning of the liquid handling system with wash cycles.

89. An apparatus as described in Claim 86 including P additional pipettes in communication with the wells, each pipette can either aspirate or dispense liquid to the wells, where P is an integer greater than or equal to 2.

90. An apparatus as described in Claim 86 including a syringe pump connected to the pipette to aspirate or dispense liquid through the pipette.

91. An apparatus as described in Claim 90 wherein the syringe pump includes a 250 microliter syringe pump.

92. An apparatus as described in Claim 80 wherein the robotic means includes a probe which, when placed in a well, identifies how much fluid is in the well.

93. An apparatus as described in Claim 86 wherein the pipette can remove tissue culture media, nutrients or proteins from a well.

94. An apparatus as described in Claim 124 wherein the biochamber includes a plate with a plurality of wells in which the cells are disposed, and the imaging means counts the number of cells in each well of the plurality of wells.

95. An apparatus as described in Claim 80 wherein the determining means analyzes tissue culture media in a well with either biochemical, immuno chemical, biological or chemical assays.

96. An apparatus as described in Claim 124 wherein the imaging means uses pattern recognition to correlate a state of a cell with a particular metabolic process of the cell.

97. An apparatus as described in Claim 80 including a determining means for automatically testing for production or degradation of proteins, simple or complex sugars, individual amino acids, individual member ions, individual molecules with respect to both physical presence and biological activity in the incubating means, said determining means connected with the incubating means, said determining means including a computer.

99. An apparatus as described in Claim 86 wherein operation of the pipette is optimized when the fluid forces applied to the cells are minimized while retaining a sufficient flow rate for medium exchange.

100. An apparatus as described in Claim 80 including a determining means for obtaining kinetic data for the rates of cell division differentiation, said determining means connected to the incubating means.

103. An apparatus as described in Claim 124 wherein the imaging means recognizes when a cell doubles in the incubating means by pattern recognition.

104. An apparatus as described in Claim 1 wherein the determining means includes a plurality of dyes, each dye associated with a different cell surface marker, to identify cell surface markers on a cell.

114. An apparatus for culturing and analyzing cells, the apparatus comprising:

a biochamber having a plurality of cell housing containers in which cells to be cultured may be introduced therein, the biochamber being a dynamically controlled closed system in which the cells are grown, the biochamber having an environment controlling means for dynamically controlling the closed environment of the biochamber;

a liquid handling system for providing exchange of media to the cells while the cells are in the biochamber, the liquid handling system in fluid communication with the plurality of cell housing containers in the biochamber;

an image recognition system for analyzing the state of each cell of the cells over time that are disposed in the plurality of cell housing containers in the biochamber, the image recognition system utilizing image recognition software;

a stage for supporting the biochamber, the biochamber, liquid handling system and image recognition system being in movable registration with respect to one another whereby the liquid handling system and image recognition system can access different cell housing containers; and

a system controller capable of regulating interaction between the biochamber, liquid handling system, image recognition system and stage.

115. The apparatus for culturing and analyzing cells according to Claim 114, wherein the image recognition system further includes a microscope comprising a camera for deriving images from the cells within the plurality of cell housing containers.

116. The apparatus for culturing and analyzing cells according to Claim 115, wherein the derived images are processed by the image recognition software to determine cellular characteristics of the cells.

117. The apparatus for culturing and analyzing cells according to Claim 116, wherein upon determination of particular cellular characteristics of the cells, the system controller is prompted to actuate the liquid handling system to provide exchange of media to the cells.

118. The apparatus for culturing and analyzing cells according to Claim 114, wherein the liquid handling system aspirates, irrigates and dispenses the media to the cells.

119. The apparatus for culturing and analyzing cells according to Claim 114, wherein the liquid handling system further includes a plurality of pipettes for providing the exchange of media to the cells, the plurality of pipettes being movable along X, Y and Z dimensions with respect to the plurality of cell housing containers.

120. The apparatus for culturing and analyzing cells according to Claim 114, wherein the stage displaces at least one of the plurality of cell housing containers with respect to the liquid handling system and the image recognition system.

121. The apparatus for culturing and analyzing cells according to Claim 114, wherein the image recognition system is capable of determining varying cellular characteristics and the system controller regulates the biochamber and liquid handling system in response to the determined cellular characteristics.

122. The apparatus for culturing and analyzing cells according to Claim 114, wherein the biochamber is respectively displaceable to both the liquid handling system and the image recognition system.

123. The apparatus for culturing and analyzing cells according to Claim 114, wherein the biochamber is displaceable along X and Y lateral dimensions and the liquid handling system and image recognition system are displaceable along a Z dimension.

124. An apparatus as described in Claim 125 wherein the determining means includes an imaging means which images said individual cell of the plurality of cells over time in the biochamber.

125. An apparatus as described in Claim 1 wherein the incubating means includes a housing having a biochamber.

126. An apparatus as described in Claim 51 wherein the incubating means includes a housing having a biochamber.

127. An apparatus as described in Claim 57 wherein the incubating means includes a housing having a biochamber.

IX. Evidence appendix

Not Applicable

X. Related proceedings appendix

Not applicable